Updates on recent guidance published and impact on GMP inspections

Vimal SACHDEVA
Technical Officer (Senior Inspector)
MHP/RPQ/PQT/INSP

Contents

1. GMP Guidelines adopted in 2021 and 2022
2. Working Documents in Public Consultation
3. New Working Documents Under Review
4. International Guidelines and Initiatives
5. Current Thinking

GMP Guidelines adopted in 2021 and 2022

Documents recently adopted for use (WHO TRS 1033, 2021)

1. Annex 1: Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations
2. Annex 2: Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation
3. Annex 3: GMP: Water for Pharmaceutical Use
4. Annex 4: Guideline on Data Integrity
5. Annex 5: WHO/UN Population Fund Recommendations for condom storage and shipping temperatures
6. Annex 6: WHO/UN Population Fund Guidance on Testing of Male Latex Condoms.

Documents recently adopted for use (WHO TRS 1033, 2021)

7. Annex 7: WHO/UN Population Fund Guidance on conducting Post-market Surveillance of condoms
8. Annex 8: WHO “Biowaiver List”: Proposal to waive in-vivo BE requirements for WHO Model List of Essential Medicines immediate-release, solid dosage forms
9. Annex 9: Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce
10. Annex 10: Good reliance practices in the regulation of medical products: high-level principles and considerations
11. Annex 11: Good regulatory practices in the regulation of medical products

Documents recently adopted for use (WHO TRS 1044, 2022)

1. Annex 1: Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations
2. Annex 2: **WHO GMP for sterile pharmaceutical products**
3. Annex 3: IAEA/WHO Guideline on GMP for Investigational Radiopharmaceutical products
4. Annex 4: WHO Guidelines on technology transfer in pharmaceutical manufacturing
5. Annex 5: WHO GMP for medicinal gases
6. Annex 6: WHO Good Practices for R&D facilities of pharmaceutical products

Documents recently adopted for use (WHO TRS 1044, 2022)

1. Annex 7: WHO GMP for investigational products
2. Annex 8: Points to consider for setting the remaining shelf-life of medical products upon delivery
3. Annex 9: WHO/UNFPA Guidance on natural rubber latex male condom stability studies
4. Annex 10: WHO/UNFPA Technical Specification for TCu380A intrauterine device
5. Annex 11: WHO Biowaiver List: proposal to waive in-vivo BE requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms

WHO TRS 1044, Annex-2 (EU & PIC/S GMP Annex-1)

Annex 2 has 10 chapters covering

1. **Introduction and scope**
2. **Principles**
3. **Pharmaceutical Quality System (PQS)**
4. **Premises**
5. **Equipment**
6. **Utilities**
7. **Personnel**
8. **Production and specific technologies**
9. **Environmental and process monitoring**
10. **Quality Control**

Aim of Final Version

- Introduce new guidance with additional details to provide further clarity in key areas.
- Align Annex-2 with other chapters and annexes of the GMP Guide which have incorporated the use of the principles of **Quality Risk Management (QRM)** and implement the elements of a **Contamination Control Strategy (CCS)** across the facility.
- Provide guidance for the use of **new technologies** such as Restricted Access Barrier Systems (RABS), isolators, robotic systems, single-use technologies, rapid microbial testing and monitoring systems.
- Provide a detailed **roadmap for manufacturers** through restructuring for a more logical flow of information.

Key Guidance (not exhaustive list !)

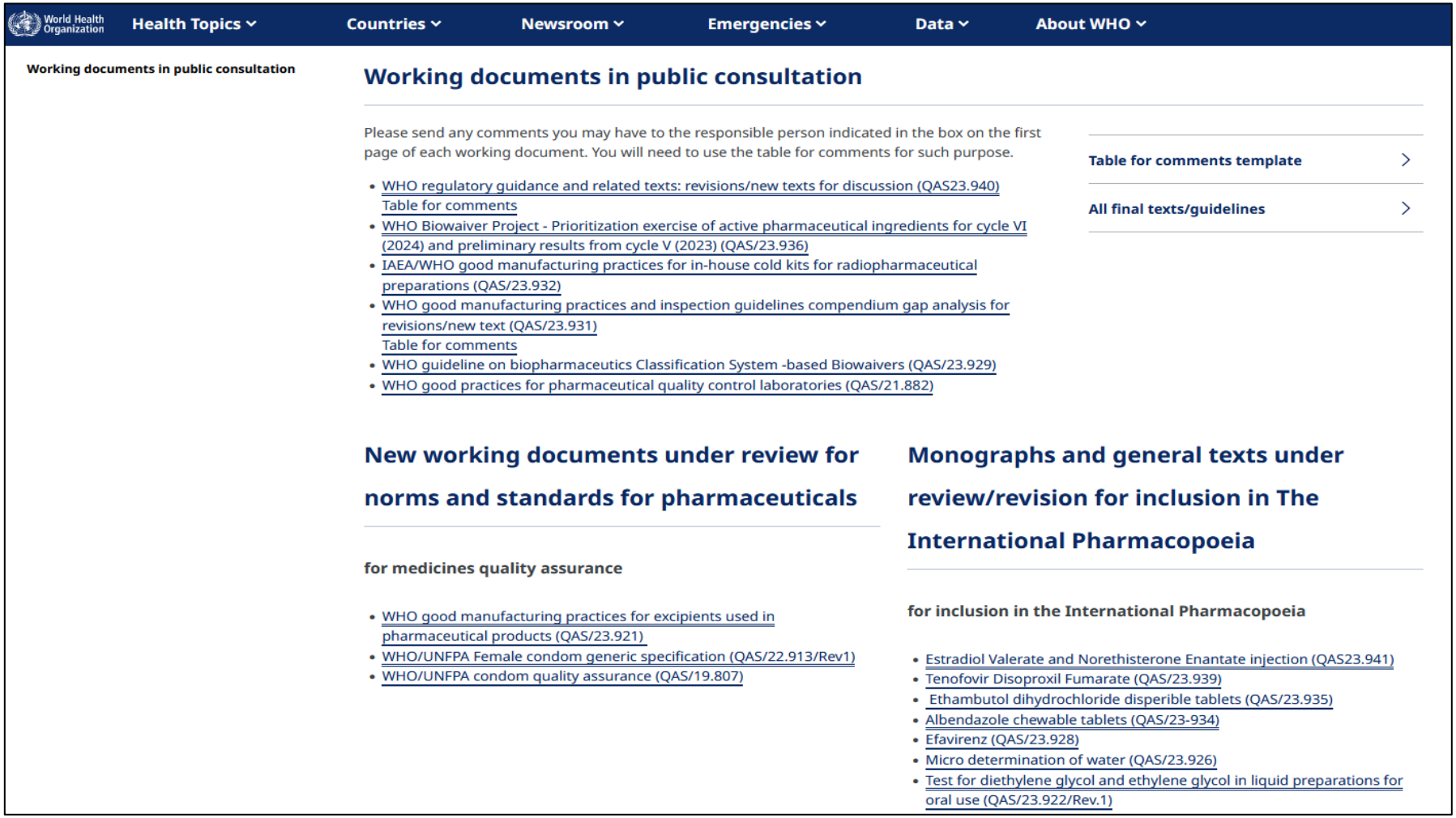
- Emphasis on ICH Q10 (Pharmaceutical Quality system)
- Emphasis on ICH Q9 (Quality Risk Management)
- Barrier technologies (Chapter 4)
- Classification clean room (Chapter 4)
- Material and Personnel Transfer (Chapter 4)
- Disinfection
- Water For Injection (Chapter 6)
- Gas filtration handling (Chapter 6)
- Steam (Chapter 6)
- Personnel (Gowning, Qualification, APS)
- Production (Lyophillisaton, BFS, FFS, SUS, Closed Systems)

Key Guidance (not exhaustive list !)

- PUPSIT
- Integrity Testing of Containers
- Microbiology monitoring
- Aseptic process simulation (APS)
- Microbiology (Chapter 10)
- Monitoring & 5 µm

Working Documents in Public Consultation and New Working Documents Under Review

Where can you find “Current projects“?



World Health Organization | Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

Working documents in public consultation

Working documents in public consultation

Please send any comments you may have to the responsible person indicated in the box on the first page of each working document. You will need to use the table for comments for such purpose.

- WHO regulatory guidance and related texts: revisions/new texts for discussion (QAS23.940)
  Table for comments
- WHO Biowaiver Project - Prioritization exercise of active pharmaceutical ingredients for cycle VI (2024) and preliminary results from cycle V (2023) (QAS/23.936)
- IAEA/WHO good manufacturing practices for in-house cold kits for radiopharmaceutical preparations (QAS/23.932)
- WHO good manufacturing practices and inspection guidelines compendium gap analysis for revisions/new text (QAS/23.931)
  Table for comments
- WHO guideline on biopharmaceutics Classification System -based Biowaivers (QAS/23.929)
- WHO good practices for pharmaceutical quality control laboratories (QAS/21.882)

Table for comments template

All final texts/guidelines

New working documents under review for norms and standards for pharmaceuticals

for medicines quality assurance

- WHO good manufacturing practices for excipients used in pharmaceutical products (QAS/23.921)
- WHO/UNFPA Female condom generic specification (QAS/22.913/Rev1)
- WHO/UNFPA condom quality assurance (QAS/19.807)

Monographs and general texts under review/revision for inclusion in The International Pharmacopoeia

for inclusion in the International Pharmacopoeia

- Estradiol Valerate and Norethisterone Enantate injection (QAS23.941)
- Tenofovir Disoproxil Fumarate (QAS/23.939)
- Ethambutol dihydrochloride disperible tablets (QAS/23.935)
- Albendazole chewable tablets (QAS/23-934)
- Efavirenz (QAS/23.928)
- Micro determination of water (QAS/23.926)
- Test for diethylene glycol and ethylene glycol in liquid preparations for oral use (QAS/23.922/Rev.1)

https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation

Working documents in public consultation

1. WHO regulatory guidance and related texts (QAS23.940)
2. WHO Biowaiver Project – prioritization exercise of active pharmaceutical ingredients for cycle VI (2024) and preliminary results from cycle V (2023) QAS/23.936
3. IAEA/WHO GMP for in-house cold kits for radiopharmaceutical preparations (QAS/23.931)
4. WHO guideline on biopharmaceutics Classification System based biowaivers (QAS/23.929)
5. WHO good practices for **pharmaceutical quality control laboratories** (QAS/21.882)

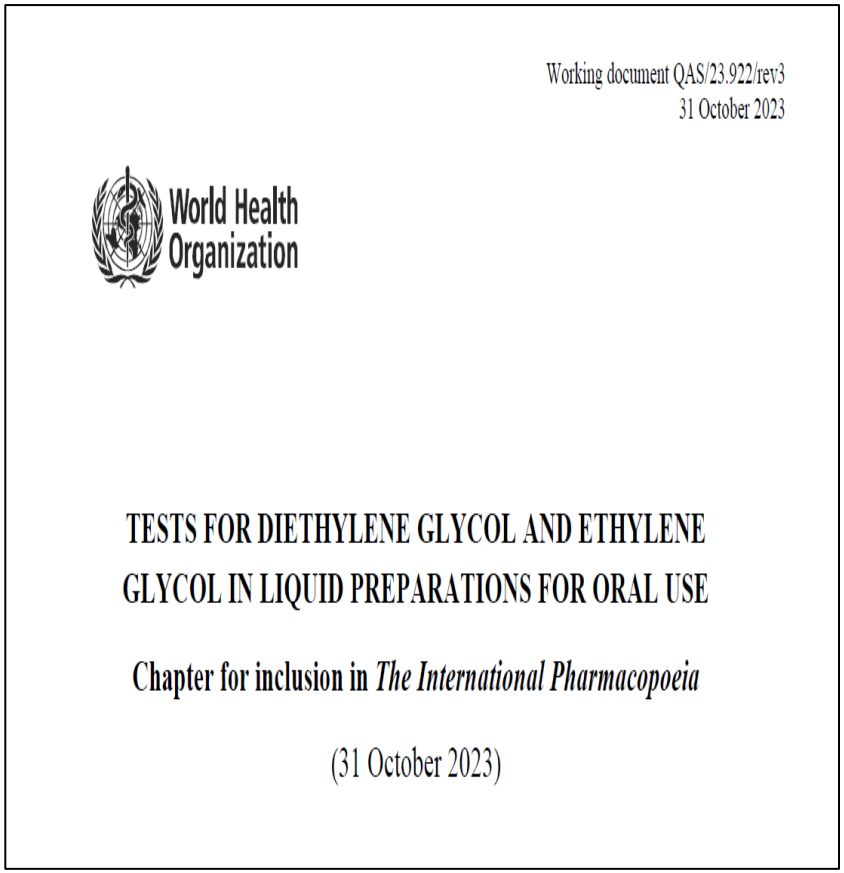
New working documents under review

1. WHO GMP for **excipients used in pharmaceutical products** (QAS/23.921)
2. WHO/UNFPA Female Condom Generic Specification (QAS/22.913/Rev1)
3. WHO/UNFPA condom quality assurance (QAS/19.807)

WHO good manufacturing practices for excipients used in pharmaceutical products – was adopted at the 57th ECSPP, 9-13 October 2023, (to be published as an annex to the meeting report), together with the ECSPP support for the development of two appendices to the guideline:

- Points to consider the document, focusing on a risk management-based approach for excipients with possible impurities;
- A list of high-risk excipients.

New Guidance Documents



Working document QAS/23.922/rev3
31 October 2023

World Health Organization

TESTS FOR DIETHYLENE GLYCOL AND ETHYLENE GLYCOL IN LIQUID PREPARATIONS FOR ORAL USE

Chapter for inclusion in *The International Pharmacopoeia*

(31 October 2023)

A recommendation was made to the WHO Norms and Standards for Pharmaceuticals (NSP) Team to develop a WHO guidance on good manufacturing practices (GMP) considerations for the prevention and control of contamination of medicines with **nitrosamines.**

Water Sanitisation and Health (WASH)

Water Sanitation and Health (who.int)

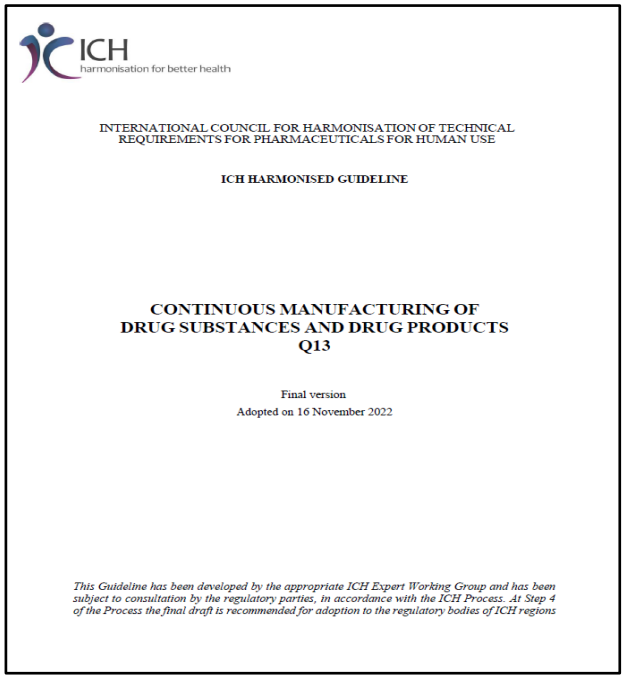
WHO Guidance on waste and wastewater management in pharmaceutical manufacturing with emphasis on antibiotic production

The purpose of this guideline is to establish an independent, scientifically derived framework for applying health-based targets for managing discharges from antibiotic manufacturing, with the intent to limit antibiotic resistance development and ecological effects caused by discharges of antibacterial agents. The guidance complements initiatives on quality and safety of antibiotics such as the WHO Good Manufacturing Practices (GMP) scheme.

International Guidelines and Initiatives

International guidelines and initiatives

Q13 Guideline on Continuous Manufacturing



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Final version
Adopted on 16 November 2022

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions

Source: "ICH Q13 Journey: From Idea to Reality", slide deck presented at International Consortium for Advanced Medicines Manufacturing by Sau Lee, USFDA April 2023.

Main Body of the Guideline

- Covers **fundamental aspects of CM** that are not specific to technology, dosage form, or molecule type
  - CM Concepts
  - Scientific Approaches
  - Regulatory Considerations

Annex I | **Annex II** | **Annex III** | **Annex IV** | **Annex V**

Provide illustrative examples and considerations specific to certain modalities (e.g., chemical entities, therapeutic proteins), technologies, and production methods

International guidelines and initiatives

Current Status of ICH Q9 Quality Risk Management

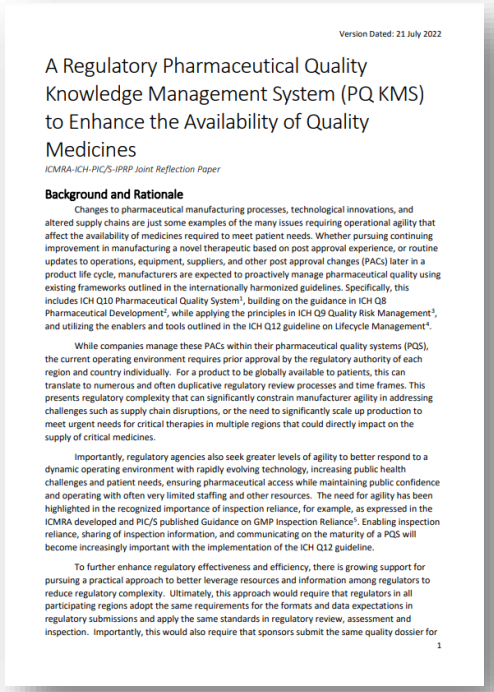
The ICH Q9(R1) Guideline reached *Step 4* of the ICH process on 18 January 2023. Foundational guideline supporting the implementation of other ICH guidelines. The WG continues to work to develop specific training materials (with examples) to supplement the existing ICH briefing pack on ICH Q9, as well as to explain and facilitate the implementation and application of the proposed revisions. Four key subject areas;

- Subjectivity in QRM
- Product Availability Risks
- Formality in QRM
- Risk-based decision-making

International guidelines and initiatives

PQKMS - A Coordinated Pharmaceutical Quality Knowledge Management Strategy

- A collective Pharmaceutical Quality Knowledge Management capability to ensure timely and complete information and assessments about the state of pharmaceutical quality management and risk management capabilities.
  - Harmonized structured and standardized electronic formats.
  - Secure sharing of information about pharmaceutical manufacturing facilities.
  - Full harmonization of data elements submitted in the quality modules of the common technical document. Simultaneous submissions within a marketing authorization application.
  - Enabling more extensive mutual reliance among regulators



Version Dated: 21 July 2022

A Regulatory Pharmaceutical Quality Knowledge Management System (PQ KMS) to Enhance the Availability of Quality Medicines

ICMRA-ICH-PIC/S-IPRP Joint Reflection Paper

Background and Rationale

Changes to pharmaceutical manufacturing processes, technological innovations, and altered supply chains are just some examples of the many issues requiring operational agility that affect the availability of medicines required to meet patient needs. Whether pursuing continuing improvement in manufacturing a novel therapeutic based on post approval experience, or routine updates to operations, equipment, suppliers, and other post approval changes (PACs) later in a product life cycle, manufacturers are expected to proactively manage pharmaceutical quality using existing frameworks outlined in the internationally harmonized guidelines. Specifically, this includes ICH Q10 Pharmaceutical Quality System[1], building on the guidance in ICH Q8 Pharmaceutical Development[2], while applying the principles in ICH Q9 Quality Risk Management[3], and utilizing the enablers and tools outlined in the ICH Q12 guideline on Lifecycle Management[4].

While companies manage these PACs within their pharmaceutical quality systems (PQS), the current operating environment requires prior approval by the regulatory authority of each region and country individually. For a product to be globally available to patients, this can translate to numerous and often duplicative regulatory review processes and time frames. This presents regulatory complexity that can significantly constrain manufacturer agility in addressing challenges such as supply chain disruptions, or the need to significantly scale up production to meet urgent needs for critical therapies in multiple regions that could directly impact on the supply of critical medicines.

Importantly, regulatory agencies also seek greater levels of agility to better respond to a dynamic operating environment with rapidly evolving technology, increasing public health challenges and patient needs, ensuring pharmaceutical access while maintaining public confidence and operating with often very limited staffing and other resources. The need for agility has been highlighted in the recognized importance of inspection reliance, for example, as expressed in the ICMRA developed and PIC/S published Guidance on GMP Inspection Reliance[5]. Enabling inspection reliance, sharing of inspection information, and communicating on the maturity of a PQS will become increasingly important with the implementation of the ICH Q12 guideline.

To further enhance regulatory effectiveness and efficiency, there is growing support for pursuing a practical approach to better leverage resources and information among regulators to reduce regulatory complexity. Ultimately, this approach would require that regulators in all participating regions adopt the same requirements for the formats and data expectations in regulatory submissions and apply the same standards in regulatory review, assessment and inspection. Importantly, this would also require that sponsors submit the same quality dossier for

1

Current Thinking

Continuous Manufacturing

- ✓ Continuous manufacturing (CM) is an innovative approach that replaces traditional batch manufacturing in the pharmaceutical industry. It involves the continuous flow of materials and processes, enabling streamlined production, improved quality control, and reduced costs.
- ✓ However, adopting CM faces challenges due to regulatory uncertainties and a lack of harmonized guidelines. Besides ICHQ13, there are no existing WHO recommendations on the subject. As this technology grows, regulators in all countries, including low and middle-income settings, should be prepared to review products and inspect sites using this technology.
- ✓ The absence of a comprehensive WHO guideline on CM may hinder global access to medicines by impeding regulatory alignment, inhibiting technology transfer, and creating barriers to entry for manufacturers in resource-limited settings.
- ✓ WHO considering developing a guidance in this area. A risk-based approach in either a reflection paper, points-to-consider document or guideline would be adopted to provide guidance to GMP inspectors as well as to the pharmaceutical industry.

Artificial Intelligence (AI)

- ✓ AI revolutionizes pharmaceutical manufacturing by enabling advanced analytics, predictive modelling, and process optimization. It can enhance the industry's efficiency, quality control, and regulatory compliance.
- ✓ However, the widespread adoption of AI in pharmaceutical manufacturing faces challenges related to regulatory frameworks, data privacy, and interoperability. The absence of comprehensive guidelines on AI in pharmaceutical manufacturing creates uncertainties and barriers to global implementation.
- ✓ Developing a WHO guideline on AI will provide a standardized framework, ensuring ethical practices and regulatory alignment and facilitating global access to safe and effective medicines.
- ✓ Currently, there is not enough clear information on AI in GMP areas. A reflection paper/point to consider could be drafted.

Conclusion

Modernisation of GMP Guidelines is an important goal. WHO TRS 1044, Annex-2 (EU GMP Annex 1) is a good example of modernisation and harmonisation across regions to provide more standardised international GMP guidelines.

Harmonisation is also achieved through international fora such as ICH for example on guidelines on Continuous manufacturing and Quality Risk Management.

ICMRA provides a strategic vision, cooperating with international organisations to achieve coordinated work plans to achieve the vision.

Thank you for your attention!

Any questions?

Vimal SACHDEVA
Technical Officer (Senior inspector)
WHO-HQ/EMP/RPQ/PQT/INSP
sachdevav@who.int